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PROTEIN HYDROLYSATES IN NUTRITIONAL EMERGENCIES

II. Clinical Studies

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PROTEIN HYDROLYSATES IN NUTRITIONAL EMERGENCIES

II. Clinical Studies

The greatly increased need for protein in a wide variety of clinical conditions has long presented a problem to the physician and dietitian who must devise suitable meals, and to the patient who must contrive to eat what appears to be, in his apathetic condition, a diet of gargantuan proportions. Fortunately for all concerned, the problem is now greatly simplified through the availability of pure proteins which may be fed, as is, or in pre-digested form to supplement the food intake. Where oral consumption is limited or entirely prohibited because of the patient's condition, pre-digested proteins are particularly invaluable because they may be administered parenterally and thus avoid taxing the gastrointestinal system.

The use of protein hydrolysates has been instrumental in saving the lives of severely wounded or extensively burned patients hitherto regarded as hopeless. The severity of surgical procedure may now be tempered with high protein therapy, the period of convalescence shortened and its storminess allayed. Like blood plasma, protein hydrolysates have aided in the recent war in rehabilitating battle wounded who formerly would have been tragically abandoned as beyond the aid of medical science.

Starvation and Nutritional Edema: Severe starvation such as has been extremely prevalent during the war may often result in almost complete functional failure of the gastrointestinal tract. This means that even if food is eventually made available to people in such advanced stages of starvation, it will be valueless because the ability to handle it has been largely lost. Fluid or food cannot be swallowed, while even tube feedings cannot always be retained but are lost through vomiting or diarrhea. It has recently been reported, however, that amino acid or protein hydrolysate therapy is capable of preventing starvation fatalities even in the late or supposedly irreversible stages of inanition (1). Kits of pre-digested proteins, vitamins, mineral salts and glucose are already being used successfully in certain areas of starvation to rehabilitate victims of severe food privation. Reports show that dying persons, totally incapable of retaining food, have responded dramatically within 24 to 48 hours to protein hydrolysate parenteral therapy and have subsequently been able to eat foods and become restored to health (2). A typical example is the work of Krishnan *et al* (3) during the 1943 famine in India. These investigators showed for the first time that the intravenous injection of hydrolyzed protein in combination with glucose solution was highly effective in preventing death from starvation and reviving patients to the point where food and fluid could be retained. Glucose, saline solution, plasma or whole blood alone was each relatively ineffective.

Nutritional edema—known also as war or famine edema, prison edema, hunger swelling—is, as the various descriptive names imply, a condition commonly resulting from starvation. It is precipitated primarily by insufficiency of protein intake, frequently in conjunction with caloric deficiency. It is manifested by swelling of various body tissues due to accumulation of fluid—the result of a drop in the concentration of blood plasma proteins. High protein diets and the administration of plasma proteins or protein hydrolysates readily restore normal equilibrium conditions*.

Surgery: Protein nutrition constitutes an extremely significant factor in the successful outcome of surgical procedure. A low level of protein nutrition during the preoperative stage increases operative risk and the chances of postoperative complications. Protein losses are considerable following surgery. Elman (4) has reported losses of from 10 to 26 grams per day of urinary nitrogen due to trauma induced by surgical manipulation, despite the administration of large amounts of glucose. Co Tui *et al* (5) and Brunschwig and associates (6) have likewise confirmed the occurrence of excessive post-operative loss of protein. Loss of plasma and plasma proteins through hemorrhage, unless counteracted by adequate protein reserves, has been shown by Marsh (7) and by Elman (8) to be an important factor in the development of acute hypoproteinemia and surgical shock. Anaesthesia is another important contributory factor in the appearance of hypoproteinemia during operation in several ways. It stimulates tissue protein breakdown (9), creates temporary anoxia with subsequent plasma loss through changes in capillary permeability, and significantly impairs liver function thereby effecting a reduction in plasma protein synthesis. Casten and associates (10) have been able to demonstrate a direct relationship between duration of anaesthesia and the incidence of plasma protein loss, irrespective of other factors such as hemorrhage and shock†.

The postoperative period is characterized by alterations in nitrogen metabolism resulting in negative balance. Urinary nitrogen losses representing body tissue losses of from 2 to 12 pounds have been observed in a study of 41 surgical patients (6). Fever, hemorrhage and surgical drainage may further contribute to nitrogen losses as may also decreased postoperative food intake and temporarily impaired utilization of food proteins. Postoperative hypoproteinemia is still further aggravated by the increased need for protein for purposes of repair. In a series of almost 300 surgical patients, nearly 200 developed various degrees of postoperative hypoproteinemia with resultant impairment of wound healing, edema, and other complications; more than half of the fatalities occurred among those patients showing pre- or post-

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**cf.—*Borden's Review of Nutrition Research,* May, 1943—"Influenc of Dietary Factors on the Regeneration of Blood Plasma Proteins."*

†50% of all patients under anaesthesia for one hour showed similar losses, while all patients under anaesthesia over 130 minutes became hypoproteinemic.

operative hypoproteinemia (11). One of the hazards of postoperative edema due to hypoproteinemia is the involvement of the lungs with consequent predisposition to fatal pneumonia or respiratory failure (12, 13, 14).

The prevention and treatment of surgical complications due to hypoproteinemia—a condition which is particularly prevalent in patients coming to surgery because of gastrointestinal disorders (14), ulcers (15, 16), cancer (17) or general causes (18)—lies in the administration of high protein (and concommitantly high carbohydrate) diets. This is most easily and economically accomplished with protein hydrolysates given orally, parenterally or by tube. Rapid and uneventful recovery from surgery as well as actual saving of lives in many instances have been attributed to the timely administration of predigested proteins (19, 20, 21).

Wounds, Fractures, Burns: The delayed recovery characteristic of hypoproteinemic surgical patients occurs also in the healing of wounds, fractures and burned tissue. As early as 1911, Clark (22) demonstrated that a low protein diet increased the period of healing in experimental wounds in dogs. More than ten years later, other investigators reported similar observations upon the delayed healing of wounds and fractures of rats (23, 24), as well as the additional observation that the bones of rats on low protein diets broke under less force than those of rats on a high protein diet. Not until 1938, however, was it demonstrated that hypoproteinemia is of considerable significance in human wound healing as well. At that time Thompson *et al* (25) noted a high incidence of postoperative wound disruption in hypoproteinemic patients compared to a low incidence in normal patients. This observation was subsequently confirmed by many others (26, 27, 28, 11). The noteworthy fact has been pointed out, however, that diets leading to hypoproteinemia are usually deficient not only in protein, but in vitamins as well and since these are important growth factors, defects in healing may be further aggravated (29). The oral and intravenous administration of hydrolyzed proteins, as well as the oral use of pure, non-hydrolyzed proteins such as milk casein, have been of particular value in the treatment and restoration of battle wounded and injured.

Moon (13) has stated that one of three developments may be expected in cases of severe burns: the patient will die of shock within 48 hours; he will succumb to and die of pneumonia, or he will recover. One of the chief factors influencing the fatal outcome of severe burns is loss of proteins, especially of plasma proteins (30).

Primarily, severe burns result in destruction of skin tissue, representing a metabolic breakdown of protein. This is followed by a heightened excretion of nitrogen in the urine (31). Taylor, Levenson and co-workers (32) have observed losses of as much as 45 grams of urinary nitrogen in 24 hours in severely burned patients—this amount being equivalent to the destruction

of 280 grams of tissue protein. In addition to protein loss from tissue destruction burns also injure skin capillaries thereby causing a loss of plasma protein from the blood vessels (33, 34). Such severe losses of protein and of blood volume as well are major factors in the induction of shock, edema and pneumonia. Shock is an abnormal phenomenon resulting largely from radical alterations in blood volume; escape of capillary fluids with subsequent accumulation in the tissues leads to edema which, in turn, if localized in the lungs, will result in pneumonia.

Intravenous injection of plasma constitutes a highly effective emergency measure in counteracting plasma losses from injured capillaries. Since transudation of plasma protein may continue for about 40 hours after a burn (35), even injected plasma may be lost unless given repeatedly in small amounts. Following restoration of normal capillary permeability, plasma transfusions are extremely helpful. Inasmuch as the protein content of plasma is only about 35 grams per 500 cc., it becomes impractical to continue plasma injections in such large amounts during convalescence when significant quantities of protein are required for tissue growth and repair as well as for maintenance of normal blood concentration. The use of protein concentrates or hydrolysates becomes particularly valuable at this time as supplements to a high protein diet. Tissue repair and healing have been shown to be markedly accelerated (16) with the use of oral and intravenous protein digests. Beling and Lee (36) have shown further that protein digests promote the healing of burned surfaces by stimulating the healing of skin grafts.

Ulcers: It has been demonstrated experimentally with rats and with dogs that a low protein diet can cause ulcers of the stomach (37, 38, 39)*. That hypoproteinemia may be a factor in human gastroduodenal ulcers has also been shown by Jones and Eaton (14) as well as others. Co Tui (40) has reported more striking remissions of gastroduodenal ulcers following therapy with a high protein, high caloric diet than with the conventional Sippy diet. The Co Tui diet supplies at least six times as much protein as the Sippy diet and twice the calories for an average 70 kg. man. It has been suggested that much of the favorable effects of protein hydrolysates used in the treatment of ulcer patients, is derived not only from the extra protein supplied, but from their marked buffering capacity which renders them natural antacids (40a, 40b).

Other Diseases: Protein metabolism plays a major role in the etiology, as well as in the course of many diseases particularly those of the liver, kidney and blood stream.

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*cf.—*Borden's Review of Nutrition Research,* November, 1945—"The Newer Knowledge of Milk in the Management of Peptic Ulcer."

(Liver): Dietary insufficiency of protein may lead to pathologic alterations of the liver. Since the liver is the main site of protein metabolism, any derangement of liver function, in turn, will be reflected in impaired protein nutrition. Thus a vicious cycle is established with ultimate development of hypoproteinemia and its common manifestations such as nutritional edema. In severe instances, particularly when proteins (such as casein) providing labile methyl groups are lacking, fatty infiltration and cirrhosis of the liver may develop (41, 42). Latest methods for treating liver cirrhosis depend upon the provision of a high protein, high vitamin and high calorie diet, as against former regimens in which attention was given only to the carbohydrate content of the diet. Clinical studies at the Mayo Clinic (43, 44) have clearly demonstrated the superiority of the newer treatment. In New York, Patek and Post (45) have similarly reported success in the dietary treatment of liver cirrhosis. Their diet was particularly rich in protein and the vitamin B complex, as well as in other nutritive essentials. By means of this diet they were able to increase the survival rate of cirrhotic patients after the onset of ascites* to 57% after one year and 45% after two years, as compared with survival rates of 39% and 21%, respectively, for control patients. They noted also improvement in liver function, disappearance of many symptoms, arrest of the disease and general bodily improvement.

These clinical studies, therefore, strongly suggest the importance of providing high protein diets, rich in carbohydrates and vitamins as well, for arresting liver disease and permitting functional regeneration of liver cells. The availability of protein concentrates such as milk casein, and of hydrolysates of milk, meat and other proteins, greatly simplifies this task as does also the availability of synthetic vitamins and vitamin concentrates.

(Kidney): Disorders of the kidney are intimately bound up with the problems of protein metabolism. Without going into detail concerning the various clinical syndromes of kidney inflammation and degeneration, it may be stated that hypoproteinemia (depletion of blood and tissue protein), proteinuria (loss of protein via the urine) and edema are common symptoms in most conditions of kidney dysfunction. For years a controversy has existed with respect to the proper dietary management of kidney disorders. Because of the impaired ability of damaged kidneys to handle the excretion products of protein metabolism, many authorities have advocated a reduction in the amount of protein provided in the diet. The possibility that a high protein diet might excessively tax even the normal kidney has also been cited. This theory has had no confirmation with respect to humans. In fact, even when up to 40% of the caloric intake is provided by protein, as is common among the Eskimos, no damage to the kidney has ever been observed; simi-

*An accumulation of fluid in the abdominal cavity.

larly, no ill effects have been reported among Arctic explorers who have subsisted exclusively on meat diets for a number of years (46).

The present medical consensus is that dietary protein requirements are particularly high in kidney disease because of the significant protein losses which are incurred. Mosenthal (47) has expressed the prevailing opinion that protein restriction is necessary—if at all—only when kidney function is severely impaired and uremia imminent. Protein needs would include, therefore, not only normal requirements of about 1 gram per kilo of body weight, but also an amount equivalent to that lost in the urine for replacement of serum albumin and for the correction of edema. Further, because of the chronic nature of kidney disease, depletion of tissue protein reserves is another common complication which must be compensated for by an increased protein intake. Poor appetite, nausea and vomiting associated with kidney disorders also combine to deplete protein reserves and constitute still another reason for increasing the prōtein intake. Injections of protein hydrolysates, plasma or human albumin solutions low in salt content are important adjuncts to dietary proteins, particularly where anorexia, nausea and vomiting interfere with normal intake.

Aldrich and Boyle (48) reported on a series of 40 nephritic children who were transferred from low protein diets to diets high in vitamins and in protein. They found that the disease was not arrested on the low protein diet and the patients all remained invalids, while on the new diet definite clinical improvement and even several cures were observed. Keutmann and McCann (49) reported similar clinical improvements when patients were given amounts of protein increasing from 40 to 200 grams per day.

In general, high protein diets, while not correcting the underlying disorder in the various renal syndromes, are effective in controlling the associated complications such as edema, hypoproteinemia, aid in maintaining nitrogen equilibrium and effect a marked improvement in the general well-being of the patient.

(Anemia): Anemia results when a deficiency of hemoglobin, of red blood cells or of both occurs. Globin, the protein component of hemoglobin, comprises about 95% of the hemoglobin molecule. The framework of the red blood cells wherein the hemoglobin is deposited is also largely protein in nature. These facts indicate the importance of dietary protein, in addition to classic iron therapy, in the treatment of anemia. The importance of protein foods in the synthesis of hemoglobin has been demonstrated experimentally by Whipple (50, 51). He found, further, that low protein diets led to reduced hemoglobin formation even in the presence of excess dietary iron (52). These findings were substantiated by Weech, Wollstein and Goettsch (53), who reported deficient production of red blood cells in dogs maintained on low protein diets. After a period of 80 days, it was found that more than

one-fifth of the nitrogen lost from the circulation was hemoglobin nitrogen. Translated into terms of actual protein loss, this represented a loss of six times as much hemoglobin as of serum albumin.

Clinically, anemia has been found to be frequently associated with nutritional edema resulting from deficient protein intake (54). Studies of plasma protein levels have also revealed a high incidence of hypoproteinemia in all types of anemias (55, 56, 57, 58, 59).

Experimentally, it has been demonstrated that food protein, protein hydrolysates or mixtures of amino acids when administered may be utilized preferentially for the manufacture of hemoglobin and secondarily for synthesis of serum proteins (60), particularly if the anemia is severe and the hypoproteinemia mild. It is conceivable, however, that if the severity of the two conditions were reversed, administered protein might be utilized for the preferential regeneration of the serum proteins.

Pregnancy, Pediatrics, Geriatrics:

Protein nutrition plays a particularly important role in such special physiological conditions such as pregnancy, early growth, and old age. Pregnancy and the period of early, rapid growth, present similarly, heightened demands for protein building material for the creation of new tissue. Although the problems of geriatrics do not normally impose an increased requirement for protein above normal levels, there is more apt to be a deficiency of protein in the older person because of decreased food intake, lack of appetite, food idiosyncrasies, difficulty in mastication and similar factors*.

Pregnancy: Hypoproteinemia is a common occurrence during pregnancy and is due primarily to the heavy drain on plasma and reserve proteins imposed by the preferential needs of the fetus (61). Alterations in total blood volume constitute a secondary cause of hypoproteinemia. Failure to ingest a diet sufficiently adequate in protein further aggravates the severity of hypoproteinemic symptoms. Recent dietary surveys (62, 63) among pregnant women have indicated a prevalence of low protein intake: in one group more than 86 per cent of the women were found to have protein intakes below National Research Council recommendations, while the average intake for the entire group was 22 per cent below (62). Impaired digestion, prolonged or severe vomiting—both frequent complications of pregnancy—are additional factors in the development of hypoproteinemia.

Hypoproteinemia during this period is frequently associated with edema (64), anemia (65, 66) and the various toxemias (67, 68) of pregnancy. Impaired absorption of vitally needed calcium may be another disturbance resulting from protein deficiency (69). Other far-reaching effects of diet on the

*cf.—*Borden's Review of Nutrition Research,* March, 1945—"Nutrition in Geriatrics."

course and outcome of pregnancy and on the condition of the infant have been elaborated in a previous issue of this Review†.

The present trend in the prevention and treatment of edema and pre-eclampsia of pregnancy is therefore, toward the use of high protein diets. A typical example is the routine placement in a well-known maternity hospital of all pre-eclamptic patients on an exclusive milk diet for 24 hours, followed by a varied diet providing 145 grams of protein daily (70). Where such high protein intakes are required, dietary supplementation with protein concentrates and hyprolysates may materially simplify the attainment of the recommended levels of protein.

Geriatrics: Stieglitz (71) has indicated that moderate protein deficiency in aging individuals may be a significant factor in the appearance of subclinical manifestations of mild anemia, undue fatigue and lassitude, and lessened vigor. For reasons previously mentioned, protein intake (as well as general food consumption) is frequently inadequate in persons over 65. Impaired digestive ability resulting from achlorhydria—a condition said to be present in more than 40 per cent of persons over 60 (72)—may render unavailable a considerable portion of whatever protein may be supplied in the diet.

Although caloric requirements are less in old age due to restricted activity, adequate protein intake must be maintained to permit maximum efficiency in the functioning of body tissues. It has been pointed out, moreover, that the provision of ample dietary protein contributes significantly to the feeling of well-being during this period of life (73).

The use of protein concentrates and hydrolysates as a means of fortifying diets for older people constitutes an important means of maintaining adequate protein nutrition, particularly when appetite is poor or digestion impaired. The recent development of a special dietary food consisting of a powdered, partially defatted milk base to provide protein, as well as the other nutrients of milk, and enriched with additional vitamins and minerals (74), is representative of a growing awareness of the importance of highly nutritious diets for older persons.

Pediatrics: In the first two years of life, serum protein levels are generally lower than normal levels in later years (75). These levels are even lower in premature infants (76). Consequently, susceptibility to nutritional edema resulting from hypoproteinemia is particularly high in younger children. Added to the fact that serum protein levels are physiologically low, inadequate intake of dietary protein is a frequent complicating factor. Dietary deficiency of protein may result from poor eating habits, lack of appetite, cer-

†*cf.*—*Borden's Review of Nutrition Research,* December, 1944—"Clinical studies on Prenatal Nutrition."

tain childhood diseases of the digestive tract (diarrhea, celiac disease, persistent vomiting), or allergy to milk. Hypoproteinemia in children is particularly serious because of the great demand for protein for growth and development. Further, subclinical protein deficiencies in children greatly decrease resistance to infections.

The use of protein hydrolysates, administered orally, as a source of nitrogen for infants and children allergic to milk was first successfully accomplished by Shohl *et al* (78). This suggested the usefulness of protein hydrolysates for all allergic individuals—infants or adults—where milk or egg could not be tolerated. Hill (79) has reported success in the protracted use of protein hydrolysates in a group of 36 infants all allergic to cow's milk. In more than half of these babies the hydrolysates was well tolerated, allergic eczema improved and weight gains were satisfactory. In their report on the use of protein hydrolysates in surgery, Beling and Lee (36) presented the case of an eight month old infant suffering from eczema and nutritional edema due to allergy to cow's milk. When it was found impossible to materially raise the plasma protein levels by any dietary means, protein hydrolysate was administered orally. At the end of a week the plasma protein level was considerably increased while after two weeks, both eczema and edema had completely disappeared.

Protein hydrolysates have been of especial value also in the treatment of underweight children suffering from lack of appetite (80) or from various kidney disorders (81, 82) or from acute gastrointestinal disorders (82).

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